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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,301	01/08/2001	Junming Le	0975.1005-008	5453

21005 7590 07/18/2002

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 07/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/756,301	Le et al
Examiner	**Art Unit**
Kar n Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above, claim(s) *16 and 33* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-15, 17-32, and 34-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 8, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5, 7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election with traverse of Group I drawn to chimeric antibodies, polypeptides and fusion proteins which bind to THF-alpha. Applicant has correctly pointed out that claim 33 was inadvertently left out of Group II. The traversal is on the grounds that the restriction is improper as it separates inventions which are related as combination and subcombination. This has been considered but not found persuasive. The restriction requirement of Paper No. 6 sets forth two groups which are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). Group II of the instant invention is drawn to a method for detecting human THF in a sample comprising the use of the antibodies of Group I. The inventions were demonstrated to be patentably distinct as the antibodies of Group I could be used in an in vivo method of treating TNF-alpha mediated diseases thereby fulfilling the requirement of part (2).

Applicant further argues that there is no additional burden associated with the examination of the method claims in addition to the product claims, as a search for the product would cover methods of using the product. The claims of Groups I and II are classified differently, necessitating different searches in the U.S. Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 1-55 are pending. Claims 16 and 33, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-15, 17-32 and 34-55 are examined on the merits.

Specification

3. The disclosure is objected to because of the following informalities:

The cross reference to related applications set forth on page 1 incorrectly claims priority to application 09/133,119 as a divisional application, which is incorrect as no restriction requirement was set forth in the '119 application

The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Figures 27 and 28 set forth amino acid and polynucleotide sequences without assigned identifiers.

Appropriate correction is required.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It claims priority as a divisional application to 09/133,119 which is incorrect for the reasons set forth above.

Information Disclosure Statement

5. Regarding the information disclosure statement filed April 2, 2002, it is noted that Applications corresponding to the recited attorney docket numbers were not present in the file

which contained two copies of 0975.1005-007 (US Application 09/756,161) and two copies of 0975.1005-006 (US Application 09/756,398). The lined-through references were not considered as they were not available to the examiner at the time of this action. Applicant is invited to provide replacement copies for consideration

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-15 and 17-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 32 recite "wherein the antibody is produced recombinantly". It is unclear how the method of producing the antibody influences the material properties of the claimed antibodies.

Claims 5 and 22 recite "physiological conditions". It is unclear if physiological conditions encompass physical conditions of osmolality and pH, such as those found in physiological saline, or if physiological conditions encompass in vivo conditions, such as those found in the peripheral blood of an animal. For purpose of examination, "physiological conditions" will be read as those found in vivo.

Claims 7 and 24 recite "high affinity". The term "high affinity" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Recitation of Ka values that are preferred embodiments, such as those given in the specification on page 61, lines 3-5, does not constitute a definition of what applicant considered "high affinity". For purpose of examination, "high affinity" will be defined as by the ability to block the activity of THF alpha in vitro.

Claim 17 is rendered vague and indefinite in the use of "cA2" as the sole means of identifying the claimed antibody. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct antibodies. Amendment of the claims to include the depository accession number or sequence identifiers is required, because deposit accession numbers and sequence identifiers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

Claims 1 and 18 are rendered vague and indefinite in the recitation of: epitope specific for human TNF alpha. It is unclear if the specificity is to be evaluated in relation to TNF alpha of other species such as rabbit or mouse, or if the specificity is to be evaluated in relation to human TNF-beta or gamma. For purpose of examination, the claims will be read as encompassing either alternative.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 11-13, 28-30 and 52-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 11, 28 and 53 are drawn to antibodies and polypeptides having a ID50 of at least 1 ug/ml, 15 ng/ml and 100 ng/ml, respectively. The specification teaches on page 53, lines 25-26 that cA2 has an ID 50 of 17 mg/ml as determined by an in vitro cytotoxicity assay. The specification sets forth on page 72 and figure 3 the results of an in vitro cytotoxicity assay with the cA2 antibody. It is noted that in figure 3 the concentration of the antibody is given in ng/ml. Claims 11-13, 28-30 and 52-54 are drawn to ID50s on the order of ug/ml and ng/ml. Given the inconsistencies within the specification, one of skill in the art would not know how to

make or use the claimed antibodies having the recited ID50 values, because one of skill in the art would not be able to ascertain the actual ID50 of the cA2 antibody. Therefore, one of skill in the art would be subject to undue experimentation in order to make and use the claimed antibodies having specific ID50 values.

10. Claims 1-10, 14, 15, 18-27, , 31, 32 and 34-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric antibodies containing all of the variable regions of the parent non-human antibody, said chimeric antibody having unspecified binding affinity for TNF alpha; the entire cA2 antibody; and antibodies comprising the entire light chain of cA2 (SEQ ID NO:3) and the entire heavy chain of cA2 (SEQ ID NO:5), does not reasonably provide enablement for antibodies or polypeptides which have only a single light or heavy chain of cA2, antibodies which compete with cA2 for binding to hTNF, chimeric antibodies which are not cA2 having Ka values of at least 1 X 10^8 L/mole or 1 X 10^9 L/mole, or fragments of antibodies or polypeptides, thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A)As drawn to chimeric antibodies other than cA2 which compete for binding with cA2 and have affinity constants of 1 X 10^8 or 1 X 10^9.

Claims 9 and 10, 26 and 27 are drawn to chimeric antibodies comprising part of a human immunoglobulin constant domain and part of a non-human variable region said antibodies binding to TNF alpha with the affinity constants of 1 X 10^8 or 1 X 10^9. Claims 8 and 25 are drawn to chimeric antibodies which competitively inhibit the binding of cA2 to TNF alpha. The specification teaches on page 81 lines 5-7 that it was an unexpected that the chimeric A2 antibody, termed the cA2 antibody, had an affinity constant that was higher than the parent murine antibody as it would be expected that a chimeric antibody would have an affinity constant that was equal to or lower than that of the parent antibody. The specification teaches that the cA2 antibody consists of both heavy and light chains of the murine A2 antibody, in addition to

the human constant regions of Ig gamma 1 and kappa. The specification provides no special teachings for how to make other chimeric anti-TNF antibodies that would duplicate the claimed high affinity constants. Further, the art teaches that chimeric and humanized antibodies often have decreased binding affinity relative to their murine counterparts (Mateo et al, Hybridoma, 2000, Vol. 19, pp. 463-471). Adair et al (WO 92/11383, reference AL4 of the IDS filed July 3, 2001) teach how to make a chimeric humanized antibody to TNF alpha, said humanized antibody comprising a human framework in which murine CDR sequences have been inserted. Adair et al point out that in order to obtain a humanized antibody having satisfactory binding affinity, it is necessary to alter certain amino acids within the framework of the variable region (page 6, last bridging paragraph). Thus, given the teachings of the specification regarding the unexpected high binding affinity of the cA2 antibody, the teachings of the recent art regarding the expectation of lower binding affinity for a chimeric antibody, and the teachings of Adair et al regarding the necessity of altering framework regions to improve binding affinity, it can be concluded that the specification is lacking in teachings on how to make other chimeric antibodies which bind to TNF alpha with the claimed affinity constants or having the ability to competitively inhibit the binding of cA2 to TNF alpha, as said inhibitor would need to possess an affinity constant of a similar order of magnitude as cA2 in order to compete with cA2 in binding to TNF alpha. Given these lack of teachings and the unpredictability of the art as exemplified by Mateo et al and Adair et al, a person of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make chimeric antibodies other than cA2 which would have the claimed affinity constants.

(B)As drawn to chimeric antibodies comprising part of SEQ ID NO:3 and part of SEQ ID NO:5, polypeptides comprising either SEQ ID NO:3 or SEQ ID NO:5, polypeptides comprising fragments of either SEQ ID NO:3 or SEQ ID NO:5 and fusion proteins comprising either SEQ ID NO:3 or SEQ ID NO:5 and fragments of said fusion proteins.

Claims 1-10, 14, 15, 18-27, 31, 32, 34-39 encompass chimeric antibodies containing less than all of the light and heavy chain variable regions of a parent non-human antibody. Claims

40-51 and 52 encompasses polypeptides comprising less than all the light chain and heavy chain variable regions. Claims 45-59 are drawn to polypeptides fragments of SEQ ID NO:3 and/or SEQ ID NO:5 which competitively inhibit the binding of cA2 to TNF alpha. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. Paul (Fundamental Immunology, (text), 1993, pages 292-293) teaches that the structure of the variable chain provides the three dimensional context in which different amino acids interact to form ligand binding sites. Paul further teaches that the CDR regions contained in the variable chain are brought together by dimerization of the heavy and light chain variable regions (page 293, first column lines 3-8) to form the ligand binding surface and that sequence variation within the CDR alters ligand recognition. Thus it cannot be expected that antibodies or polypeptide comprising less than the full variable regions of SEQ ID NO:3 and SEQ ID NO:5 will form an identical ligand binding surface. Further the result of altering the sequence context around the CDR cannot be anticipated as the relative positions and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. Paul further teaches that CDR loops can interact with framework regions as evidenced by work with humanized antibodies (page 293, second column, lines 9-12). It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having antigen-binding function. Thus the proper association and sequence context of the heavy and light chain variable regions is required in order to form functional antigen binding sites. It is unlikely that antibodies, polypeptides or fusion proteins as defined by the claims which contain less than the full heavy and light chain variable regions of the cA2 antibody and fused to any human framework sequence or comprised by any polypeptide sequence would have the required binding function. The specification provides no direction or guidance regarding how to produce fusion

proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanized antibody can be obtained by replacing the CDR regions of an acceptor human antibody with the CDRs of murine anti-TNF alpha antibody. It is noted that the specification does not identify CDR residues in SEQ ID NO:3 or SEQ ID NO:5. As evidenced by Adair et al. (WO 92/11383) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (page. 4, last paragraph). Adair et al demonstrates that amino acid residues in the framework region are involved in antigen binding by a humanized anti-TNF alpha antibody (page 6, last paragraph to page 7, line 4).

Thus, there is no support in the specification for a nexus between the properties of the cA2 antibody to any or all of the myriad antibodies and polypeptides which are encompassed within this language. With regard to claims 45-49 drawn to polypeptides comprising either SEQ ID NO:3 or 5 or fragments of SEQ ID NO:3 or 5, there is no written description in the specification for how to make said polypeptides, nor is it reasonable to conclude that they would compete with cA2 for binding to THF alpha, for the reasons set forth in this section and the additional reasons set forth in section (A) above. One of skill in the art would neither expect nor predict the appropriate functioning of the antibodies or polypeptides as broadly as is claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to chimeric antibodies containing a portion of a variable region and polypeptides comprising portions of SEQ ID NO:3 and/or SEQ ID NO:5.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169, reference AX4 of the IDS filed July 9, 2001) in view of Zerler (EP 380,068, reference AP of the IDS filed July 9, 2001) as evidenced by Morrison et al (In: Antibody Engineering, (monograph) 1995, Ed. Borrebaeck, page 291).

Claim 1 is drawn to a chimeric antibody comprising at least a part of a human immunoglobulin constant region and at least a part of a non-human variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor alpha. Claim 18 is drawn to the chimeric antibody of claim 1 with the added embodiment of IgG1 as the human constant region. Claims 2 and 19 specifically embody the antibodies of claims 1 and 18, respectively, wherein the binding of said antibodies to TNF alpha inhibits a pathological activity of TNF alpha. Claims 4 and 21 specifically embody the antibodies of claims 1 and 18, respectively, wherein said chimeric antibody two light and two heavy chains comprising at least a part of a constant region and a part of a variable region. Claims 5 and 22 specifically embody the

chimeric antibodies of claims 1 and 18, respectively, wherein said antibody neutralizes TNF alpha under physiological conditions. Claims 6 and 23 further embody a variable region of murine origin for the antibodies of claims 1 and 18, respectively. Claims 7 and 24 further specify that the antibodies of claims 1 and 18 are derived from a high affinity murine monoclonal antibody which binds to a neutralizing epitope of TNF alpha. Claims 14 and 31 specifically embody the antibodies of claims 1 and 18 in detectably labeled form; claims 15 and 32 specifically embody the chimeric antibodies of claims 1 and 18 which are produced recombinantly.

Moller et al teach the murine mAb 195 (page 163, first column under "Production of Monoclonal Antibodies") which specifically binds to an epitope of TNF alpha that is present on human TNF alpha and Chimpanzee TNF alpha and does not show any cross-reactivity with other human proteins including TNF-beta (page 164, second column under the heading "Characterization of Monoclonal antibodies by Immunoblot" and page 165 first column, lines 3-5). Moller et al teach that mAb 195 neutralized the cytotoxic activity of human TNF alpha in vitro (page 164, first column and Table 2, second column). Moller et al also teach that administration of the mAb 195 to mice injected with human TNF alpha blocked the lethal effect of TNF in the mice (page 165, second column, under the heading "Neutralization of Human TNF Alpha in the Mouse). Additionally the mAb 195 was detectably labeled with biotin (page 167, first column under the heading of "Biotinylation of Monoclonal Antibodies") thus fulfilling the embodiments of claims 14 and 31. Thus, Moller et al teach a murine antibody which specifically binds to an epitope of human TNF alpha, wherein said antibody is a high affinity murine monoclonal antibody (defined as by the ability to block the activity of THF alpha in vitro as stated in the rejection under 35 U.S.C. 112, 2nd paragraph, section 6, above), and the inhibition of a pathological activity of TNF alpha (TNF-induced lethality), the neutralization of TNF alpha under physiological conditions (within the mouse). Moller et al do not teach a chimeric antibody comprising part of a human constant region, nor a human IgG1 constant region.

Zerler et al teach a chimeric antibody comprising part of a human constant region derived from murine antibodies which bind to the Il-2 receptor. Zerler et al teach a general method for how to make recombinant chimeric antibodies comprising a IgG1 human constant regions (page 5, lines 53-55) and murine variable regions. Zerler et al suggest that chimeric antibodies against TNF can be made in a similar method (page 10, line 55 to page 11, line 8). Zerler et al teach the expression of the vector encoding the chimeric antibodies in mammalian cell lines transformed by said vector (claim 13). Zerler et al do not specifically teach that the recombinant chimeric antibody obtained from the disclosed method would contain two light chains and two heavy chains. Morrison et al teach (page 291, under the heading "Things to Consider") that transfectomas generally secrete IgGs as H2L2 (two heavy chains and two light chains). Thus, it would be reasonable to assume that the transformed mammalian cells taught by Zerler et al secrete chimeric antibodies having two light chains and two heavy chains.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a chimeric antibody having a IgG1 constant region, wherein the variable region was derived from mAb195. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Zerler et al regarding the advantages of chimeric antibodies versus murine antibodies such as the elimination of allergic side effects and the increase in serum half live (page 3, lines 29-33), and the suggestion of Zerler et al, that the disclosed methods of making the recombinant chimeric antibodies could be applied to antibodies against TNF. Zerler et al specifically teach that an antibody having a human IgG1 constant region has a serum half-life of 21-23 whereas a murine antibody has a serum half life of 15-16 hours.

13. Claims 1-7, 15, 18-24 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moller et al (Cytokine, 1990, Vol. 2, pp. 162-169) and Zerler (EP 380,068) and Morrison et al (In: Antibody Engineering, (monograph) 1995, Ed. Borrebaeck, page 291) as applied to claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 above, and further in view of Socher et al (PNAS, 1987, Vol.

84, pp. 8829-8833) as evidenced by the abstract of Goh (Annals of the Academy of Medicine, 1990, Vol. 19, pp. 235-239). The specific embodiments of claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 are set forth in the rejection above.

Claims 3 and 20 specifically embody the chimeric antibodies according to claims 1 and 18 wherein said antibodies do not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO:1.

For the reasons stated in the above rejection the combination of Moller et al and Zerler et al render obvious the chimeric antibodies which bind to a specific epitope of TNF alpha, inhibit a pathological activity of TNF alpha, and neutralize TNF alpha under physiological conditions. Neither Moller et al nor Zerler et al teach specific epitopes of TNF alpha to which the antibodies do not bind.

Socher et al teach polyclonal antibodies raised against fragments of human tumor necrosis factor. Socher et al do not specifically state that the tumor necrosis factor was TNF alpha. However, Socher et al identify said tumor necrosis factor as a cytokine secreted by activated macrophages which is identical to the protein termed cachectin, said protein being a mediator of endotoxin induced shock. It is known in the art that TNF alpha is synonymous with cachectin and is a product of macrophages, being the principal effector of septic shock, as set forth in the abstract of Goh. Therefore, it is reasonable to conclude that the tumor necrosis factor of Socher et al is TNF alpha. Socher et al teach that antiserum raised in rabbits to peptides of hTNF consisting of residues 65-79, 98-111 and 124-141 neutralized the cytolytic activity of hTNF in vitro and inhibited the binding to hTNF to the TNF receptor (Table 2). These peptides represent epitopes that are encompassed by claims 3 and 20 as these antibodies bind in between residues 55 and 154.

Socher et al teach that the biological activities of TNF alpha comprise endotoxin induced shock and the induction of cachexia (page 8829, column 1, first paragraph under the abstract). Socher et al teach that the binding of TNF to cell surface receptors is necessary for the induction

of the biological activity of TNF and that blocking of said binding will inhibit the biological activities of TNF.

Moller et al teach the mAb195 antibody which neutralizes the cytotoxic activity of TNF alpha in vitro and inhibits the lethality of TNF alpha in vivo. Moller et al further teach that the antibodies mAb114 and mAb199 bind to hTNF but neutralize TNF very weakly or do not neutralize TNF at all (abstract) and that both of these antibodies fail to inhibit the lethality of TNF alpha (page 165, second column under the heading "Neutralization of Human TNF alpha in the mouse") in vivo. Thus Moller et al teach a nexus between an antibodies ability to neutralize TNF in vitro and inhibit a TNF alpha pathology in vivo.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute murine monoclonal antibodies raised to the peptides of hTNF consisting of residues 65-79, 98-111 and 124-14. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Moller et al on the nexus between the ability of an antibody to neutralize TNF cytolytic activities in vitro and the ability of said antibody to inhibit a TNF induced pathology in vivo and the teachings of Socher et al on the potent neutralization of cytolytic activity attributes to antibodies which bind in between residues 55 and 154 of TNF alpha.

Double Patenting

14. a rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

15. Claims 34-36, 38, 39, 46 and 47 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 3 and 5-9 of prior U.S. Patent No. 6,284,471. This is a double patenting rejection.

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. a terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 4, 15, 18, 21, 32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 5-7 of U.S. Patent No. 6,284,471. Although the conflicting claims are not identical, they are not patentably distinct from each other because the chimeric antibodies of the '471 patent anticipate the genus of chimeric antibodies claimed in the instant specification.

18. Claims 1, 4, 6, 8, 15, 18, 21, 23, 25, 32, 34-40, 48, 49 and 55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 and 38 of copending Application No. 09/756,161. Although the conflicting claims are not identical, they are not patentably distinct from each other because the humanized antibodies of the '161 application represent species which anticipate the chimeric antibodies of instant claims 1, 4, 6, 8, 15, 18, 21, 23, 25, 32 and 34-39 which are drawn to antibodies having at least a portion of a non-human variable region. Further, the instant claims 40, 48, 49 and 55, drawn to polypeptides comprising a fragment of SEQ ID NO:3 or SEQ ID NO:5, can be anticipated by claims 17-22 of the '161 application drawn to humanized light and heavy chains and claims 1-16, 23, 24 and 32, drawn to antigen-binding fragments of the humanized antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 17, 37, 40-45, 50-55 are rejected under the judicially created doctrine of double patenting over claims 1, 3 and 5-9 of U. S. Patent No 6,284,471. since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: cA2 antibody which is encompassed as a species in claims 1, 3 and 5-9 of the '471 patent; the chimeric antibody of claim 37 would be encoded by the polynucleotides of claim 7 of the '471 patent; the polypeptides comprising SEQ ID NO:3 or SEQ ID NO:5 of claims 8 and 9 of the '471 patent anticipate the polypeptides of instant claims 40-45, 50-55 as the properties of neutralizing TNF, inhibiting TNF, not binding to epitopes 11-13, 37-42, 49-57 or 155-157 are disclosed in the '471 patent.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application

which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

20. All claims are rejected.

Conclusion

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

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July 15, 2002